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Design, synthesis, crystal structure and fungicidal activity of (*E*)-5-(methoxyimino)-3,5-dihydrobenzo[*e*][1,2]oxazepin-4(1*H*)-one analogues†‡

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A practical method of four-step synthesis towards novel (*E*)-5-(methoxyimino)-3,5-dihydrobenzo[*e*][1,2]-oxazepin-4(1*H*)-one antifungals is presented, where a commercially available pesticide and pharmacology intermediate, (*E*)-methyl 2-(2-(bromomethyl)phenyl)-2-(methoxyimino)acetate (**1**), was used as starting material. These compounds were confirmed by ¹H NMR, ¹³C NMR, high-resolution mass spectroscopy and X-ray crystal structure. *Via in vitro* fungicidal evaluation, the moderate to high activities of several compounds against eight phytopathogenic fungi were demonstrated. Especially, the fungicidal activities of compounds **5-03** and **5-09** were comparable to those of the controls azoxystrobin and trifloxystrobin in precise virulence measurements for four fungi. These results suggested that dihydrobenzo[*e*][1,2]oxazepin-4(1*H*)-one analogues could be considered as potential fungicidal candidates for crop protection.

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Introduction

Among the oxazepine compounds, benzoxazepinones and their derivatives have a central place in pharmaceutical chemistry.¹ For example, GSK'481 (**I**) is a highly potent and mono-selective receptor interacting protein 1 kinase;² neochromine S5 (**II**) can inhibit proliferation and increase apoptosis of activated T cells;³ GDC-0032 (**III**) is a β -sparing phosphoinositide 3-kinase inhibitor and has been evaluated as potential treatment for human malignancies;⁴ tetrahydropyrazolo-oxazepinone (**IV**) derivatives as potential telomerase inhibitors exhibit high anticancer activity⁵ (Fig. 1). As such, all these representative compounds containing benzoxazepinone moiety reportedly show outstanding biological activity.

Consequently, the wide practical interest in this important heterocyclic ring system motivates continuous efforts of the exploitation of both efficient compounds and synthetic methods, but almost all reported benzoxazepinones are 1,4-benzoxazepinones.^{6–12} From comprehensive literature search and analysis, we find that the 1,2-benzoxazepinone skeleton is a new fragment. A method to synthesize a variety of 1,2-

benzoxazepinones, where N–O bonds are adjacent to carbonyl groups, is lacking.

On the basis of the development of fungicides targeted at cytochrome bc1 complex^{13,14} and prompted by the excellent biological activity of trifloxystrobin and fluoxastrobin, we attempted to investigate and optimize the structure of strobilurins, and target compounds were designed and synthesized. These compounds were evaluated against eight phytopathogenic fungi. In this work, we present a mild and convenient synthesis as well as systemic bioactivity investigations of this new variety of (*E*)-5-(methoxyimino)-3,5-dihydrobenzo[*e*][1,2]oxazepin-4(1*H*)-one (**5**), which has nearby hetero-atoms (N and O) in the seven-membered ring (Scheme 1). Meanwhile, the corresponding chemical problems and the structure–activity relationships are discussed.

Fig. 1 Biologically active compounds containing benzoxazepinone moiety.

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Scheme 1 Strategies for the target compound design.

Results and discussion

Chemistry

The specific synthetic route to compounds 4 and 5 from the commercially available starting material is depicted in Scheme 2. Precursor 3 was prepared as reported in the literature.¹⁵ Starting material 1 was reacted with *N*-hydroxyphthalimide to give intermediate 2, the latter being hydrazinolized to produce the key precursor 3. Initial studies found that substrate 3 reacted without any additive giving compound 4 in a yield of only 7% at room temperature (RT) for 4 hours. We began our investigations by choosing 3 as the exclusive substrate for optimizing the reaction conditions. Firstly, the reaction temperature was investigated (Table 1, entries 2, 3). It was found that the yield at reflux temperature (15%) is a little higher than that at RT (9%) after as long as 24 hours of reaction, where majority of substrate remained unconverted for these conditions. Then, some organic and inorganic bases were screened. NaOMe furnished good yield, at reflux for 4 hours, whereas other bases, such as Et₃N, NaOH and K₂CO₃, gave either low product yields or more byproduct.

The present optimized synthesis of benzoxazepinone 4 involved stirring of 3 with NaOMe in methanol at reflux for 4 hours. The method was amenable to gram-scale synthesis under optimized conditions. NaOMe stimulated the cleavage of a molecule of methanol in the intramolecular cyclization procedure. Compound 4 was obtained with good yields. Then compound 4 was reacted with various halides in DMF in the presence of NaH to afford corresponding compounds 5. Most of compounds 5 were obtained in moderate to good yields. However, the synthetic yields of compounds 5-06 and 5-12 were only 34% and 24%, the reason being that compounds 5-06 and 5-12 could be further alkylated to give double substituted compounds 5-16 and 5-17, respectively

(Scheme 2). In addition, the structure of 5 was further identified by X-ray diffraction studies (Fig. 2).

Crystal structure analysis. To provide more evidence for the proposed molecular structure and establish the conformation of the target compounds, compound 5-09 was recrystallized by slow evaporation from a dichloromethane/*n*-hexane (1 : 5 v/v) solution. Single-crystal X-ray diffraction analysis showed that the crystal structure of compound 5-09 belongs to the orthorhombic system, space group *P*2₁2₁2₁. The details of the crystallographic data and structure refinement parameters are summarized in Tables S1–S7.† The molecular structure of compound 5-09 is shown in Fig. 2. The seven-membered ring appears to be twisted and the double bonds C(1)=O(2) and C(2)=N(2) in compound 5-09 are pushed in opposite directions. The bond lengths of compound 5-09 are within the normal range.

Structure–activity relationship (SAR). (*E*)-Methyl 2-(2-(bromomethyl)phenyl)-2-(methoxyimino)acetate (1), a bromoalkane with bromobenzyl group and 2-(methoxyimino)-acetate group, as the starting material, which has been mass-produced, is an essential intermediate of agricultural fungicides originating in natural product strobilurin A, becoming an attractive area of research in pharmaceutical and agricultural chemistry.¹⁶ Furthermore, it is not only widely used as key intermediate in fungicide synthesis but also serves as a scaffold to access other pesticides.¹⁷ Fungicides with this intermediate have proved to be of broad spectrum, high efficiency and low toxicity as determined through field experiments and all kinds of toxicity tests.¹⁸ Compounds 4 and 5 not only keep the important scaffold of methoxyacrylates, including benzene ring, methoxyimino and carbonyl, but also combine two heteroatoms (N,O) into one molecule which plays an important role in biological activity.^{19,20} Accordingly, fungicidal activity of these compounds was tested against eight phytopathogenic fungi.

The antifungal activities of the title compounds (compounds 5-01 to 5-19) were measured *in vitro* and the corresponding results are summarized in Table 2. Byproducts 5-16 and 5-17 were tested under the same conditions as well. In general, most of the compounds displayed considerable to excellent fungicidal activities against eight phytopathogens except compounds 5-07, 5-15, 5-18 and 5-19. Most of these compounds were highly active against *Phytophthora*

Scheme 2 Preparation of title compounds.

Table 1 Optimization of the reaction conditions for the cyclization of **3** to afford **4**

Entry	Base	Temperature	Time (h)	Yield (%) ^a
1	—	RT	4	7
2	—	RT	24	9
3	—	Reflux	24	15
4	NaOMe	RT	8	57
5	NaOMe	Reflux	4	81
6	Et ₃ N	Reflux	4	45
7	NaOH	Reflux	4	67
8	Na ₂ CO ₃	Reflux	4	56

^a Isolated yield.

infestans, *Pythium aphanidermatum*, *Setosphaeria turcica* and *Pyricularia grisea* *in vitro* at 50 µg mL⁻¹. Compounds **5-16** and **5-17** exhibited certain fungicidal activities. No obvious difference of fungicidal activity between aliphatic and aromatic series was observed. For aliphatic series (compounds **5-01** to **5-07**, **5-18** and **5-19**), however, the fungicidal activity is determined by the length of the aliphatic chain, where title compounds with shorter aliphatic chain exhibited lower bioactivity than those with longer chain, *i.e.* compounds: **5-18** < **5-19** < **5-01** < **5-02** < **5-03** ≈ **5-04** ≈ **5-05** (Fig. 3). For the benzene substituent of aromatic series (compounds **5-08** to **5-12**), a *para*-substituent (*para*-alkyl of compound **5-08**, *para*-Cl of compound **5-09**, *para*-nitro of compound **5-10** and *para*-cyano of compound **5-11**), no matter it being electron-withdrawing (-Cl, -nitro and -cyano) or electron-donating (-alkyl), was the most important factor to enhance the bioactivity compared with *ortho*-substituent (*ortho*-alkyl of compound **5-12**). In contrast, for the hetero-aromatic series (compounds **5-13** and **5-14**), the inhibitory rate was lower than that of benzene substituent series. In all, several compounds displayed higher activity than commercial fungicides (azoxystrobin and trifloxystrobin), including compounds **5-03**, **5-08**, and **5-09** against *Phytophthora infestans* and compounds **5-03** to **5-05**, **5-08** to **5-11** against *Setosphaeria turcica*. The inhibitory rates of compounds **5-03**

to **5-05**, **5-08** to **5-11** were comparable to those of azoxystrobin and trifloxystrobin against *Pyricularia grisea* and *Colletotrichum orbiculare*.

In order to study the activities of the superior target compounds further, five compounds were chosen for precise virulence measurements for four of the fungi, and their EC₅₀ values are summarized in Table 3. These compounds were highly effective against *Setosphaeria turcica* and compounds **5-03**, **5-05** and **5-09** exhibited lower EC₅₀ values (greater anti-fungal activity) than the controls azoxystrobin and trifloxystrobin. Compound **5-03** was effective against *Phytophthora infestans*, *Pyricularia grisea* and *Setosphaeria turcica* with EC₅₀ values of 17.8, 26.1 and 9.6 µg mL⁻¹, respectively. Compound **5-09** displayed excellent activities against *Sclerotinia sclerotiorum*, *Phytophthora infestans*, *Pyricularia grisea* and *Setosphaeria turcica* with EC₅₀ values of 21.7, 15.0, 16.7 and 7.8 µg mL⁻¹, respectively.

In conclusion, several compounds displayed comparable activity to the commercial fungicides (azoxystrobin and trifloxystrobin) against some fungi. In particular, compounds **5-03** and **5-09** showed better bioactivities than the other compounds against most phytopathogens, suggesting they might deserve to be developed as potential agricultural fungicides.

Quantitative structure–activity relationship (QSAR) analyses. During biological screening, models of the new compounds were constructed using topomer CoMFA with Sybyl 7.3 to find the relationship between structure and activity in theory. A cross-validation q^2 value of 0.594 and a non-cross-validation r^2 value of 0.899 with an optimized component of 3 were obtained, which suggested that the model has good predictive ability ($q^2 > 0.5$). The sterically favoured and disfavoured regions are shown in green and yellow. For the electrostatic field, the positively charged favoured regions are shown in blue, and the negatively charge favoured regions are shown in red.

In contour maps of aliphatic series, the length of the R group of compounds **5-03** to **5-05** was comparable to aromatic substituent and compounds **5-03** to **5-05** also exhibited excellent fungicidal activity. For the benzene substituent of

Fig. 2 X-ray crystal structure of **5-09** (CCDC-1518111).

Table 2 *In vitro* fungicidal activity of target compounds against phytopathogens^a

Compound	Mycelium growth inhibitory rate (%) at 50 $\mu\text{g mL}^{-1}$							
	SS	BC	PI	PA	RS	ST	PG	CO
4	22.8	5.0	11.7	2.9	8.6	36.7	14.0	15.3
5-01	NA	20.3	24.2	9.6	10.0	26.8	21.9	19.1
5-02	13.3	27.5	35.5	22.3	20.0	45.4	35.9	22.1
5-03	60.0	40.6	56.5	46.2	35.0	69.2	51.6	36.8
5-04	57.3	40.6	48.4	40.1	33.3	65.7	50.0	38.2
5-05	58.7	40.6	37.1	35.5	25.0	70.0	53.1	36.8
5-06	15.6	12.8	23.3	11.0	10.9	15.3	16.1	14.7
5-07	NA	NA	NA	11.0	NA	25.4	3.2	5.1
5-08	65.3	36.2	58.1	40.1	28.0	56.9	46.9	32.4
5-09	72.0	40.6	56.5	54.7	28.3	67.7	62.5	32.4
5-10	22.7	31.9	46.8	41.2	25.0	65.7	51.6	25.0
5-11	41.3	36.4	52.5	42.3	35.0	62.3	50.7	29.4
5-12	15.4	5.2	18.2	4.7	11.7	14.4	13.4	5.7
5-13	41.7	29.7	30.1	34.3	24.6	49.2	35.5	15.3
5-14	17.3	34.8	35.5	23.8	16.7	42.2	29.7	17.6
5-15	NA	7.3	9.2	7.6	4.6	15.8	14.5	10.2
5-16	5.6	4.4	5.7	4.9	5.7	24.2	19.4	5.7
5-17	14.3	15.1	25.5	25.6	7.4	27.1	22.0	17.0
5-18	13.6	13.0	8.9	9.3	1.7	19.8	5.4	5.1
5-19	6.1	9.6	25.2	5.2	15.4	30.5	4.8	6.8
Azoxystrobin	98.7	72.5	56.5	57.3	43.3	49.5	53.1	36.8
Trifloxystrobin	99.6	49.3	53.2	62.5	41.7	54.9	50.0	23.5

SS = *Sclerotinia sclerotiorum* (Lib.) de Bary; BC = *Botrytis cinerea*; PI = *Phytophthora infestans* (Mont.) De Bary; PA = *Pythium aphanidermatum*; RS = *Rhizoctonia solani*; ST = *Setosphaeria turcica*; PG = *Pyricularia grisea*; CO = *Colletotrichum orbiculare* (Berk. & Ment.). ^a NA: no activity.

aromatic series, compounds with a *para*-substituent showed better fungicidal activity than compounds with an *ortho*-substituent. Compound **5-09**, which has the highest activity, was selected as a representative molecule, making it is easier to explain the contour map. The benzene ring of benzoxazepinone moiety with small substituent exhibits stronger bioactivities in the map of the steric field (Fig. 4a). In the electrostatic field, the carbonyl group of benzoxazepinone moiety be covered with red blocks (Fig. 4b), indicating the electro-negativity was beneficial for antifungal activity. In Fig. 4c, reducing the steric hindrance of benzyl was beneficial to the activity and a large substituent such as a *tert*-butyl group or a cyclohexyl group in the *para* position of benzene ring was unfavorable. *Para*-position of benzene ring be covered with blue blocks in the electrostatic field (Fig. 4d), indicating the introduction of an electropositive group was beneficial for antifungal activity. The above discussions about SARs are conducive to further structure optimization of this series of compounds.

Fig. 3 Inhibitory rates of selected compounds against PI, ST and PG.

Experimental

Instrumentation and materials

¹H NMR and ¹³C NMR spectra were obtained at 300 MHz using a Bruker Avance DPX300 spectrometer in CDCl₃ or DMSO-*d*₆ solution with tetramethylsilane as the internal standard. Chemical shift values (δ) are given in parts per million. High-resolution mass spectrometry data were obtained with an Accurate-Mass-Q-TOF MS 6520 system equipped with an electrospray ionization (ESI) source. The single-crystal structure analysis was performed using X-ray diffraction with a Thermo Fisher ESCALAB 250 diffractometer. Melting points were determined with a Cole-Parmer microscope melting point apparatus and are uncorrected. Intermediate 3 was synthesized according to a literature report.²¹ All the title compounds were confirmed by ¹H NMR, ¹³C NMR and HRMS.

Synthetic procedures

Optimized synthetic procedure for compound 4. Compound 3 (50 mmol) and methanol (50 mL) were stirred in an

Table 3 EC₅₀ values of target compounds against four fungi

Compound	EC ₅₀ ($\mu\text{g mL}^{-1}$)			
	SS	PI	PG	ST
5-03	38.9	17.8	26.1	9.6
5-04	47.2	35.9	35.4	16.1
5-05	43.0	>100	25.3	6.5
5-09	21.7	15.0	16.7	7.8
5-11	75.0	40.0	55.5	23.5
Azoxystrobin	1.8	12.2	21.0	15.1
Trifloxystrobin	1.6	18.0	18.4	16.9

Fig. 4 Topomer CoMFA contour maps of compound 5-09. (a) Steric field around benzoxazepinone moiety. (b) Electrostatic field around benzoxazepinone moiety. (c) Steric field around R group (4-ClC₆H₄CH₂). (d) Electrostatic field around R group (4-ClC₆H₄CH₂).

ice bath. Sodium methoxide (2.67 g, 50 mmol) was added slowly and then the reaction mixture was heated to reflux for 4 h. After cooling, the solid was filtered off, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel using petroleum ether/ethyl acetate (EtOAc:PE = 3:1) as eluent to give compound 4 (81%).

Data for (*E*)-5-(methoxyimino)-3,5-dihydrobenzo[*e*][1,2]oxazepin-4(1*H*)-one (4). Yield 81%; white solid; mp 146 °C. ¹H NMR (300 MHz, DMSO) δ 11.63 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.42 (dt, *J* = 7.6, 3.8 Hz, 1H), 7.32 (t, *J* = 7.1 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 5.19 (s, 2H), 3.90 (s, 3H). ¹³C NMR (75 MHz, DMSO) δ 168.42, 136.45, 130.44, 130.11, 126.53, 125.92, 124.63, 76.08, 62.52. HRMS (ESI) *m/z* calcd for C₁₀H₁₀N₂O₃ (M + H)⁺ 207.0764, found 207.0765.

General procedure for the preparation of title compounds

5. Intermediate 4 (3 mmol) was dissolved in DMF (10 mL), and a catalytic amount of KI was added to the mixture, followed by the addition of 60% NaH (0.18 g, 4.5 mmol) at 10 °C. The reaction was allowed to stir for 1 h at this temperature. A solution of halides (3.3 mmol) in 2 mL of DMF was then added dropwise to the mixture, and the progress of the reaction was monitored by thin-layer chromatography. Upon completion, 30 mL H₂O was added to the mixture, then extracted by ethyl acetate (3 × 60 mL) and the organic layer concentrated to an oil. The pure compounds 5 were obtained by column chromatography (EtOAc:PE = 4:1) purification.

Data for (*E*)-5-(methoxyimino)-3-propyl-3,5-dihydrobenzo[*e*][1,2]oxazepin-4(1*H*)-one (5-01). White crystal; yield, 52%; mp 83–85 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.80 (d, *J* = 7.6 Hz, 1H), 7.46–7.31 (m, 2H), 7.13 (d, *J* = 7.7 Hz, 1H), 5.23 (s, 2H), 4.08 (s, 3H), 3.84–3.53 (m, 2H), 1.80 (tt, *J* = 14.3, 7.1 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 167.27, 152.38, 135.28, 130.84, 129.60, 126.24, 124.86, 124.60,

74.26, 62.62, 47.50, 19.90, 10.93. HRMS (ESI) *m/z* calcd for C₁₃H₁₆N₂O₃ (M + H)⁺ 249.1234, found 249.1234.

Data for (*E*)-3-butyl-5-(methoxyimino)-3,5-dihydrobenzo[*e*][1,2]oxazepin-4(1*H*)-one (5-02). Yield 57%; white solid; mp 54–55 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.88–7.71 (m, 1H), 7.40 (ddd, *J* = 20.1, 9.9, 3.9 Hz, 2H), 7.13 (d, *J* = 7.7 Hz, 1H), 5.24 (s, 2H), 4.09 (s, 3H), 3.81–3.62 (m, 2H), 1.77 (dt, *J* = 15.0, 7.6 Hz, 2H), 1.44 (dq, *J* = 14.7, 7.3 Hz, 2H), 1.00 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 167.23, 152.38, 135.28, 130.86, 129.59, 126.24, 124.88, 124.59, 74.28, 62.62, 45.69, 28.59, 19.68, 13.40. HRMS (ESI) *m/z* calcd for C₁₄H₁₈N₂O₃ (M + H)⁺ 263.1390, found 263.1391.

Data for (*E*)-5-(methoxyimino)-3-pentyl-3,5-dihydrobenzo[*e*][1,2]oxazepin-4(1*H*)-one (5-03). Yield 69%; colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.77–7.66 (m, 1H), 7.41–7.18 (m, 2H), 7.06 (d, *J* = 7.5 Hz, 1H), 5.16 (s, 2H), 4.00 (s, 3H), 3.70–3.54 (m, 2H), 1.84–1.60 (m, 2H), 1.45–1.19 (m, 4H), 0.88 (t, *J* = 6.8 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 167.05, 152.39, 135.29, 130.71, 129.55, 126.13, 124.76, 124.63, 74.16, 62.48, 45.76, 28.47, 26.12, 21.91, 13.54. HRMS (ESI) *m/z* calcd for C₁₅H₂₀N₂O₃ (M + H)⁺ 277.1547, found 277.1547.

Data for (*E*)-3-hexyl-5-(methoxyimino)-3,5-dihydrobenzo[*e*][1,2]oxazepin-4(1*H*)-one (5-04). Yield 75%; colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.71 (d, *J* = 7.6 Hz, 1H), 7.40–7.16 (m, 2H), 7.04 (d, *J* = 7.6 Hz, 1H), 5.14 (s, 2H), 3.98 (s, 3H), 3.71–3.48 (m, 2H), 1.68 (dd, *J* = 14.2, 7.1 Hz, 2H), 1.39–1.20 (m, 6H), 0.86 (t, *J* = 6.6 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 167.06, 152.38, 135.29, 130.71, 129.54, 126.12, 124.77, 124.62, 74.17, 62.46, 45.79, 31.02, 26.39, 26.00, 22.07, 13.59. HRMS (ESI) *m/z* calcd for C₁₆H₂₃N₂O₃ (M + H)⁺ 291.1703, found 291.1702.

Data for (*E*)-3-heptyl-5-(methoxyimino)-3,5-dihydrobenzo[*e*][1,2]oxazepin-4(1*H*)-one (5-05). Yield 73%; colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.82–7.60 (m, 1H), 7.41–7.15 (m, 2H), 7.03 (d, *J* = 7.6 Hz, 1H), 5.13 (s, 2H), 3.98 (s, 3H), 3.74–3.51 (m, 2H), 1.79–1.60 (m, 2H), 1.41–1.18 (m, 8H), 0.85 (t, *J* = 6.7 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 167.03, 152.38, 135.29, 130.69, 129.51, 126.10, 124.77, 124.61, 74.16, 62.43, 45.76, 31.23, 28.49, 26.43, 26.28, 22.13, 13.64. HRMS (ESI) *m/z* calcd for C₁₇H₂₅N₂O₃ (M + H)⁺ 305.1860, found 305.1864.

Data for (*E*)-3-allyl-5-(methoxyimino)-3,5-dihydrobenzo[*e*][1,2]oxazepin-4(1*H*)-one (5-06). Yield 34%; white solid; mp 62–63 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.79 (d, *J* = 7.6 Hz, 1H), 7.38 (dq, *J* = 14.2, 6.4 Hz, 2H), 7.13 (d, *J* = 7.5 Hz, 1H), 5.96 (ddt, *J* = 16.5, 10.1, 6.3 Hz, 1H), 5.38 (ddd, *J* = 13.6, 11.1, 1.1 Hz, 2H), 5.24 (s, 2H), 4.34 (d, *J* = 6.2 Hz, 2H), 4.09 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 167.35, 152.22, 135.36, 130.80, 130.63, 129.66, 126.22, 124.75, 124.69, 119.43, 74.79, 62.65, 48.80. HRMS (ESI) *m/z* calcd for C₁₃H₁₄N₂O₃ (M + H)⁺ 247.1077, found 247.1078.

Data for (*E*)-5-(methoxyimino)-3-(prop-2-yn-1-yl)-3,5-dihydrobenzo[*e*][1,2]oxazepin-4(1*H*)-one (5-07). Yield 52.5%; yellowish solid; mp 82–83 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.67–8.55 (m, 1H), 7.96 (s, 1H), 7.55–7.34 (m, 2H), 7.22 (d, *J* = 6.8 Hz, 1H), 5.26 (d, *J* = 15.0 Hz, 1H), 5.06 (d, *J* = 15.0 Hz, 1H), 4.77

(dd, $J = 61.2, 2.6$ Hz, 2H), 4.08 (d, $J = 12.2$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 159.64, 157.22, 143.08, 135.42, 131.15, 129.91, 126.97, 124.23, 123.79, 123.01, 89.08, 65.23, 62.98. HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 245.0921, found 245.0921.

Data for (*E*)-5-(methoxyimino)-3-(4-methylbenzyl)-3,5-dihydrobenzo[*e*][1,2]oxazepin-4(1*H*)-one (5-08). Yield 50.9%; white solid; mp 72–74 °C. ^1H NMR (300 MHz, CDCl_3) δ 7.90–7.70 (m, 1H), 7.42–7.31 (m, 4H), 7.21 (d, $J = 7.9$ Hz, 2H), 7.01 (d, $J = 7.1$ Hz, 1H), 4.98 (s, 2H), 4.84 (s, 2H), 4.09 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 167.47, 152.28, 137.54, 135.42, 131.63, 130.89, 129.56, 129.07, 128.65, 126.20, 124.82, 124.57, 74.80, 62.70, 49.64, 20.84. HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 311.1390, found 311.1390.

Data for (*E*)-3-(4-chlorobenzyl)-5-(methoxyimino)-3,5-dihydrobenzo[*e*][1,2]oxazepin-4(1*H*)-one (5-09). Yield 75%; white solid; mp 93–94 °C. ^1H NMR (300 MHz, CDCl_3) δ 7.84–7.64 (m, 1H), 7.37–7.25 (m, 6H), 6.98 (d, $J = 6.4$ Hz, 1H), 4.95 (s, 2H), 4.77 (s, 2H), 4.03 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 167.66, 152.02, 135.14, 133.78, 133.24, 130.92, 130.03, 129.68, 128.60, 126.31, 124.72, 124.60, 74.83, 62.76, 49.27. HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{15}\text{ClN}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 331.0844, found 331.0847.

Data for (*E*)-5-(methoxyimino)-3-(4-nitrobenzyl)-3,5-dihydrobenzo[*e*][1,2]oxazepin-4(1*H*)-one (5-10). Yield 56%; yellowish solid; mp 92–93 °C. ^1H NMR (300 MHz, DMSO) δ 8.39–8.20 (m, 2H), 7.66 (dd, $J = 12.7, 4.9$ Hz, 3H), 7.49 (td, $J = 7.6, 1.4$ Hz, 1H), 7.38 (t, $J = 6.9$ Hz, 1H), 7.27 (d, $J = 7.8$ Hz, 1H), 5.33 (s, 2H), 5.06 (s, 2H), 3.95 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ 166.11, 152.38, 147.24, 143.36, 135.97, 130.49, 130.28, 129.47, 126.65, 125.86, 124.37, 123.92, 74.00, 62.68, 48.10. HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_5$ ($\text{M} + \text{H}$) $^+$ 342.1086, found 342.1084.

Data for (*E*)-4-((5-(methoxyimino)-4-oxo-4,5-dihydrobenzo[*e*][1,2]oxazepin-3(1*H*)-yl)methyl)benzonitrile (5-11). Yellowish oil; yield 26%. ^1H NMR (300 MHz, CDCl_3) δ 7.89–7.75 (m, 1H), 7.70 (d, $J = 8.4$ Hz, 2H), 7.54 (d, $J = 8.4$ Hz, 2H), 7.46–7.33 (m, 2H), 7.07 (d, $J = 6.6$ Hz, 1H), 5.08 (s, 2H), 4.92 (s, 2H), 4.09 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 167.80, 151.71, 140.07, 134.84, 132.22, 130.96, 129.80, 129.05, 126.46, 124.63, 124.60, 118.14, 111.79, 74.73, 62.84, 49.48. HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{16}\text{N}_3\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 322.1186, found 322.1185.

Data for (*E*)-3-(2-chlorobenzyl)-5-(methoxyimino)-3,5-dihydrobenzo[*e*][1,2]oxazepin-4(1*H*)-one (5-12). Yield 24%; white solid; mp 69–70 °C. ^1H NMR (300 MHz, CDCl_3) δ 7.90 (d, $J = 8.0$ Hz, 1H), 7.60–7.50 (m, 1H), 7.41 (dd, $J = 8.1, 5.6$ Hz, 2H), 7.32 (t, $J = 6.4$ Hz, 2H), 7.29 (s, 1H), 7.15 (d, $J = 7.6$ Hz, 1H), 5.38 (s, 2H), 5.23 (s, 2H), 4.09 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 171.17, 147.18, 137.83, 133.12, 132.63, 130.31, 129.92, 129.34, 129.23, 129.15, 126.49, 125.88, 125.07, 71.84, 67.44, 62.82. HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{15}\text{ClN}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 331.0844, found 331.0843.

Data for (*E*)-3-((2-chlorothiazol-5-yl)methyl)-5-(methoxyimino)-3,5-dihydrobenzo[*e*][1,2]oxazepin-4(1*H*)-one (5-13). Yield 66%; yellowish solid; mp 109–111 °C. ^1H NMR (300 MHz, CDCl_3) δ 7.75 (d, $J = 7.7$ Hz, 1H), 7.58 (s, 1H), 7.36 (dt, $J = 20.5, 6.7$ Hz, 2H), 7.09 (d, $J = 7.5$ Hz, 1H), 5.19 (s, 2H), 4.92 (s, 2H), 4.05 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 168.12, 152.45, 151.55, 141.23, 134.91, 133.22, 130.89, 129.82, 126.37, 124.73, 124.50, 75.08, 62.83, 42.28. HRMS (ESI) m/z calcd for $\text{C}_{14}\text{H}_{12}\text{ClN}_3\text{O}_3\text{S}$ ($\text{M} + \text{H}$) $^+$ 338.0361, found 338.0367.

Data for (*E*)-3-((6-chloropyridin-3-yl)methyl)-5-(methoxyimino)-3,5-dihydrobenzo[*e*][1,2]oxazepin-4(1*H*)-one (5-14). Yield 68%; yellowish solid; mp 109–111 °C. ^1H NMR (300 MHz, CDCl_3) δ 8.45 (d, $J = 2.4$ Hz, 1H), 7.84–7.71 (m, 2H), 7.46–7.31 (m, 3H), 7.07 (d, $J = 7.3$ Hz, 1H), 5.09 (s, 2H), 4.84 (s, 2H), 4.07 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 168.01, 151.67, 151.10, 149.71, 139.17, 134.82, 130.93, 129.79, 129.41, 126.43, 124.66, 124.56, 124.14, 74.84, 62.84, 46.73. HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{15}\text{ClN}_3\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 332.0796, found 332.0792.

Data for (*E*)-methyl 2-(methoxyimino)-2-((*E*)-5-(methoxyimino)-4-oxo-4,5-dihydrobenzo[*e*][1,2]oxazepin-3(1*H*)-yl)methyl-phenylacetate (5-15). Yield 63%; white solid; mp 147 °C. ^1H NMR (300 MHz, CDCl_3) δ 7.79–7.66 (m, 1H), 7.55–7.37 (m, 3H), 7.35–7.25 (m, 2H), 7.19 (dd, $J = 5.4, 3.6$ Hz, 1H), 6.94 (d, $J = 7.7$ Hz, 1H), 4.77 (s, 2H), 4.68 (s, 2H), 4.04 (s, 3H), 3.95 (s, 3H), 3.64 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 167.76, 162.98, 152.13, 148.36, 135.70, 133.15, 130.79, 130.49, 129.82, 129.47, 129.36, 128.45, 127.79, 126.03, 124.77, 124.62, 75.01, 63.46, 62.71, 52.48, 48.45. HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_6$ ($\text{M} + \text{H}$) $^+$ 412.1503, found 412.1503.

Data for (*E*)-1,3-diallyl-5-(methoxyimino)-3,5-dihydrobenzo[*e*][1,2]oxazepin-4(1*H*)-one (5-16). Yield 42%; white solid; mp 52 °C. ^1H NMR (300 MHz, CDCl_3) δ 7.61 (dd, $J = 6.3, 2.8$ Hz, 1H), 7.35 (ddd, $J = 3.9, 3.2, 1.1$ Hz, 2H), 7.22–7.06 (m, 1H), 6.13 (ddd, $J = 17.2, 10.2, 7.0$ Hz, 1H), 5.96–5.66 (m, 1H), 5.54–5.36 (m, 2H), 5.36–5.17 (m, 2H), 5.11 (d, $J = 7.0$ Hz, 1H), 5.00 (d, $J = 14.9$ Hz, 1H), 4.82 (d, $J = 14.9$ Hz, 1H), 4.61 (dd, $J = 15.1, 4.7$ Hz, 1H), 3.96 (d, $J = 1.0$ Hz, 3H), 3.44 (dd, $J = 15.1, 8.2$ Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 162.86, 154.10, 136.19, 133.16, 131.77, 130.73, 129.02, 127.25, 125.41, 119.11, 119.06, 90.77, 69.03, 62.06, 46.37. HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 287.1390, found 287.1391.

Data for (*E*)-1,3-bis(2-chlorobenzyl)-5-(methoxyimino)-3,5-dihydrobenzo[*e*][1,2]oxazepin-4(1*H*)-one (5-17). Yield 54%; white solid; mp 96–97 °C. ^1H NMR (300 MHz, CDCl_3) δ 7.85–7.74 (m, 1H), 7.68 (dd, $J = 5.8, 3.3$ Hz, 1H), 7.42–7.23 (m, 7H), 7.22–7.09 (m, 3H), 6.24 (s, 1H), 5.19–5.01 (m, 2H), 4.80 (d, $J = 14.9$ Hz, 1H), 4.31 (d, $J = 15.5$ Hz, 1H), 3.91 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 164.96, 154.11, 135.48, 133.75, 133.23, 133.19, 133.14, 130.61, 130.19, 129.89, 129.34, 129.28, 129.02, 128.63, 128.30, 127.62, 127.49, 126.71, 126.55, 125.89, 89.11, 72.15, 62.17, 44.21. HRMS (ESI) m/z calcd for $\text{C}_{24}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 455.0924, found 455.0930.

Data for (*E*)-5-(methoxyimino)-3-methyl-3,5-dihydrobenzo[*e*][1,2]oxazepin-4(1*H*)-one (5-18). Yield 83%; white solid; mp 106–107 °C. ^1H NMR (300 MHz, CDCl_3) δ 7.85–7.70 (m, 1H), 7.39 (ddd, $J = 15.3, 10.5, 4.3$ Hz, 2H), 7.13 (d, $J = 7.6$ Hz, 1H), 5.24 (s, 2H), 4.08 (s, 3H), 3.32 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 167.36, 152.08, 135.24, 130.88, 129.63, 126.27, 124.82, 124.65, 73.65, 62.69, 32.44. HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 221.0921, found 221.0919.

Data for (E)-3-ethyl-5-(methoxyimino)-3,5-dihydrobenzo[e][1,2]oxazepin-4(1H)-one (5-19). Yield 63%; white solid; mp 61–62 °C. ^1H NMR (300 MHz, CDCl_3) δ 7.79 (d, J = 6.8 Hz, 1H), 7.45–7.31 (m, 2H), 7.13 (d, J = 7.7 Hz, 1H), 5.25 (s, 2H), 4.08 (s, 3H), 3.77 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 167.38, 152.40, 135.34, 130.89, 129.59, 126.23, 124.94, 124.58, 74.57, 62.65, 40.94, 11.68. HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 235.1070, found 235.1070.

X-ray diffraction

Compound 5-09 was recrystallized by slow evaporation from a dichloromethane/*n*-hexane (1:5 v/v) solution to afford a single crystal suitable for X-ray crystallography and mounted in inert oil and transferred to the cold gas stream of the diffractometer. Cell dimensions and intensities were measured using a Thermo Fisher ESCALAB 250 diffractometer with graphite monochromated Mo K α radiation. Compound 5-09: orthorhombic, a = 8.7758(3) Å, b = 10.3761(4) Å, c = 16.7996(6) Å, U = 1529.75(10) Å 3 , T = 104.8, space group $P2_12_12_1$ (no. 19), Z = 4, $\mu(\text{Mo K}\alpha)$ = 0.267. A total of 6446 reflections were measured, of which 3009 were unique (R_{int} = 0.0255) in the range of $6.54 < 2\theta < 52^\circ$ ($-10 \leq h \leq 10$, $-12 \leq k \leq 10$, $-20 \leq l \leq 20$), and 3009 observed reflections with $I > 2\sigma(I)$ were used in the refinement on F^2 . The structure was solved by direct method with the SHELXTL-97 program. All of the non-H atoms were refined anisotropically by full-matrix least-squares to give the final $wR(F_2)$ = 0.0675. The atomic coordinates for 5-09 have been deposited at the Cambridge Crystallographic Data Centre. CCDC-1518111 contains the supplementary crystallographic data for this paper.

Biological assays

Fungicidal activity. The test fungi *Sclerotinia sclerotiorum* (Lib.) de Bary, *Botrytis cinerea*, *Phytophthora infestans* (Mont.) De Bary, *Pythium aphanidermatum*, *Rhizoctonia solani*, *Setosphaeria turcica*, *Pyricularia grisea* and *Colletotrichum orbiculare* (Berk. & Ment.) were provided by the Laboratory of Institute of Plant Protection, Chinese Academy of Agricultural Sciences. After retrieval from the storage tube, the strains were incubated in PDA at 25 °C for several days to get new mycelia for the antifungal assay.²² Azoxystrobin and trifloxystrobin, gifts from Jiangsu Frey Chemicals Co., were used as controls. The synthesized compounds and controls were dissolved in DMSO to prepare 20 mg·mL $^{-1}$ stock solutions before mixing with molten agar. The media containing compounds at a concentration of 50 $\mu\text{g}\cdot\text{mL}^{-1}$ for initial screening were then poured into sterilized Petri dishes for the initial screening. Their relative inhibition ratio (%) was calculated using the following equation

$$\frac{(\text{colony diameter of control} - \text{colony diameter of treatment})}{(\text{colony diameter of control} - \text{mycelial disk diameter})} \times 100\%.$$

This experiment was conducted twice with three replicates. The fungicidal activities are listed in Table 2.

A 20 mg·mL $^{-1}$ stock solution was diluted with PDA to obtain a series of concentrations, repeating the experiments above, and the inhibition rate calculated separately. The EC_{50} values were calculated by spss statistics v17.0 and listed in Table 3.

QSAR analyses

Topomer CoMFA (in the SYBYL X 7.3 program) was used to analyze the relationship between structure and activity. Topomer CoMFA is an alignment-independent 3D-QSAR method that combines the topomer search method²³ with the conventional CoMFA method. Besides the core of the molecule, we split the functional of each compound into two R groups that refer to the R $_1$ (benzoxazepinone moiety) and R $_2$ (R substituent) groups. In total, 20 compounds obtained from synthesis were used to create a data set in which the inhibition rate of all compounds was determined (Table 1) against *Setosphaeria turcica*. Three-dimensional structures of the target compounds were built by Chem3D software version 12.0.

Conclusions

In summary, we provide a novel and scalable method to prepare (E)-5-(methoxyimino)-3,5-dihydrobenzo[e][1,2]-oxazepin-4(1H)-one through a commercially available intermediate as raw material. Compound 3 underwent an efficient intramolecular cyclization and provided good isolated yields of 4 under optimized reaction conditions. Interestingly, some of these compounds displayed excellent agricultural fungicidal activities, even comparing with recent commercial products. Overall, we report a practical way to access these benzoxazepinones for their novel structure and fungicidal activities that could be of great utility for pharmacists as new scaffolds for SAR studies of their nitrogen- and oxygen-containing heterocycles, and clearly point out the direction of the optimization of better fungicide candidates. Thus, this work is significantly important for new pesticide design and development.

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Notes and references

- (a) V. G. Noskov, L. N. Kalinina, M. N. Noskova, Y. L. Kruglyak, O. G. Strukov and A. P. Bezrukovet, *Pharm. Chem. J.*, 1997, 31, 431–434; (b) L. Simon, F. Fülöp, G. Bernáth, G. Argay, A. Kálmán and P. Sohár, *Acta Pharm. Hung.*, 1996, 66, 111–118; (c) J. Frost, P. Lardenois, J. Bertin, A. Saarmets and C. Rousselle, EP, EP0351282, 1993; (d) P. Evans, E. J. Thomas and R. H. Davies, EP, EP1294697, 2003; (e) M.

- Takahashi, S. Onizawa and T. Satoh, *Bull. Chem. Soc. Jpn.*, 1974, 47, 2724–2726; (f) M. Ozeki, A. Muroyama, T. Kajimoto, T. Watanabe, K. Wakabayashi and M. Node, *Synlett*, 2009, 11, 1781–1784; (g) A. T. Taher and L. W. Mohammed, *Arch. Pharmacol. Res.*, 2013, 36, 684–693; (h) Y. Davion, G. Guillaumet, J. M. Leger, C. Jarry, B. Lesur and J. Y. Merour, *Heterocycles*, 2004, 63, 1093–1112.
- 2 P. A. Harris, B. W. King, D. Bandyopadhyay, S. B. Berger, N. Campobasso and C. A. Capriotti, *J. Med. Chem.*, 2016, 59, 2163–2178.
 - 3 Z. Gao, Y. Ma, D. Zhao, X. Zhang, H. Zhou and H. Liu, *Biochem. Pharmacol.*, 2014, 92, 358–368.
 - 4 C. O. Ndubaku, T. P. Heffron, S. T. Staben, M. Baumgardner, N. Blaquiere and E. Bradley, *J. Med. Chem.*, 2013, 56, 4597–4610.
 - 5 X. H. Liu, Y. M. Jia, B. A. Song, Z. X. Pang and S. Yang, *Bioorg. Med. Chem. Lett.*, 2013, 23, 720–723.
 - 6 (a) R. G. Shi, X. H. Wang, R. Liu and C. G. Yan, *Chem. Commun.*, 2016, 52, 6280–6283; (b) V. Psarra, M. A. Foustieris, L. Hennig, M. Bantzi, A. Giannis and S. S. Nikolaropoulos, *Tetrahedron*, 2016, 72, 2376–2385; (c) F. Li, M. Mu, N. Yang, L. Zhong, R. Hu and J. Li, *Chin. J. Org. Chem.*, 2016, 36, 1419–1425.
 - 7 (a) K. Woydowski and J. Liebscher, *Tetrahedron*, 1999, 55, 9205–9220; (b) M. Brindisi, S. Gemma, G. Alfano, G. Kshirsagar, E. Novellino and G. Campiani, *Tetrahedron Lett.*, 2013, 54, 5387–5390; (c) M. Babazadeh, R. Hosseinzadeh-Khanmiri and S. Zakhireh, *Appl. Organomet. Chem.*, 2016, 30, 514–518.
 - 8 (a) A. V. Sapegin, S. A. Kalinin, A. V. Smirnov, M. V. Dorogov and M. Krasavin, *Eur. J. Org. Chem.*, 2015, 6, 1333–1340; (b) A. F. Donnell, C. Michoud, K. C. Rupert, X. Han and D. Aguilar, *J. Med. Chem.*, 2013, 56, 7772–7787.
 - 9 (a) C. Rui, X. Jie, N. Yong, H. F. Xu, Z. Min and T. Xu, *Bioorg. Med. Chem.*, 2016, 24, 1741–1748; (b) C. L. Chen, C. C. Lee, F. L. Liu, T. C. Chen and A. A. Ali, *Eur. J. Med. Chem.*, 2016, 117, 70–84.
 - 10 (a) P. T. Kaye and M. J. Mphahlele, *Synth. Commun.*, 1994, 24, 1971–1978; (b) A. J. Fugard, B. K. Thompson, A. M. Slawin, J. E. Taylor and A. D. Smith, *Org. Lett.*, 2015, 17, 5824–5827.
 - 11 A. J. Cocuzza, D. R. Chidester, B. C. Cordova, R. M. Klabe, S. Jeffrey and S. Diamond, *Bioorg. Med. Chem. Lett.*, 2001, 11, 1389–1392.
 - 12 (a) A. A. Santilli, D. H. Kim and S. V. Wanser, *J. Heterocycl. Chem.*, 1972, 9, 309–313; (b) F. De Moliner, M. Bigatti, C. De Rosa, L. Banfi, R. Riva and A. Basso, *Mol. Diversity*, 2014, 18, 473–482.
 - 13 (a) P. L. Zhao, F. Wang, M. Z. Zhang, Z. M. Liu, W. Huang and G. F. Yang, *J. Agric. Food Chem.*, 2008, 56, 10767–10773; (b) L. Li, M. Li, H. Chi, J. Yang, Z. Li and C. Liu, *J. Fluorine Chem.*, 2016, 185, 173–180; (c) M. Liu, Y. Liu, S. Zhou, X. Zhang, S. Yu and Z. Li, *Chem. Res. Chin. Univ.*, 2016, 1–7; (d) Y. Q. Xie, Z. L. Huang, H. D. Yan, J. Li, L. Y. Ye and L. M. Che, *Chem. Biol. Drug Des.*, 2014, 85, 743–755.
 - 14 X. Yuan, C. Jia, Y. Ma, D. Yang, C. Rui and Z. Qin, *RSC Adv.*, 2016, 6, 19916–19922.
 - 15 (a) Y. L. Jiang, D. J. Krosky, L. Seiple and J. T. Stivers, *J. Am. Chem. Soc.*, 2005, 127, 17412–17420; (b) I. H. Kim, I. H. Lee, H. Nishiwaki, B. D. Hammock and K. Nishi, *Bioorg. Med. Chem.*, 2014, 22, 1163–1175.
 - 16 (a) R. López-Moreno, J. V. Mercader, C. Agulló, A. Abad-Somovilla and A. Abad-Fuentes, *Org. Biomol. Chem.*, 2013, 11, 7361–7371; (b) C. Hao, J. L. Taylor and S. R. Abrams, *Bioorg. Med. Chem. Lett.*, 2007, 17, 1979–1983; (c) S. Tu, Y. Q. Xie, S. Z. Gui, L. Y. Ye, Z. L. Huang and Y. B. Huang, *Bioorg. Med. Chem. Lett.*, 2014, 24, 2173–2176; (d) R. López-Moreno, J. V. Mercader, C. Agulló, A. Abad-Somovilla and A. Abad-Fuentes, *Food Chem.*, 2014, 152, 230–236; (e) W. Jiang, F. Hu, H. Gu, W. Chuan and F. Xu, *Chin. J. Org. Chem.*, 2014, 34, 774–782.
 - 17 (a) H. PEI, M. X. Ou, J. Y. Wang, K. Yu, M. X. Lin and P. A. Liu, *Nongyaoxue Xuebao*, 2009, 11, 208–212; (b) J. M. Clough, C. R. A. Godfrey, F. De, J. P. Hutchings, G. M. Anthony and M. Vivienne, *Eur. Pat.*, 278595, 1988.
 - 18 (a) H. Sauter, W. Steglich and T. Anke, *Angew. Chem., Int. Ed.*, 1999, 38, 1328–1349; (b) D. W. Bartlett, J. M. Clough, J. R. Godwin, A. A. Hall, M. Hamer and B. Parr-Dobrzanski, *Pest Manage. Sci.*, 2002, 58, 649–662.
 - 19 N. Kuntala, J. R. Telu, V. Banothu, S. B. Nallapati, J. S. Anireddy and S. Pal, *Med. Chem. Commun.*, 2015, 6, 1612–1619.
 - 20 D. Stumpfe and J. Bajorath, *Med. Chem. Commun.*, 2016, 7, 1045–1055.
 - 21 Y. Li, H. Q. Zhang, J. Liu, X. P. Yang and Z. J. Liu, *J. Agric. Food Chem.*, 2006, 54, 3636–3640.
 - 22 X. J. Yan, W. C. Qin, L. P. Sun, S. H. Qi, D. B. Yang, Z. H. Qin and H. Z. Yuan, *J. Agric. Food Chem.*, 2010, 58, 2720–2725.
 - 23 W. Ding, M. Sun, S. Luo, T. Xu, Y. Cao, X. Yan and Y. Wang, *Molecules*, 2013, 18, 10228–10241.